Corticosteroid switch after progression on abiraterone acetate plus prednisone

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Abstract

Introduction Abiraterone acetate plus prednisone is approved in metastatic castration-resistant prostate cancer. There is some evidence in favour of the steroid switch from prednisone to dexamethasone in patients who progressed whilst on abiraterone acetate plus prednisone or prednisolone.

Materials and Methods The aim of this review is to discuss the results from the clinical studies available, examining potential mechanisms of action and patient selection criteria for this treatment option.

Results A total of four studies were evaluated. Among possible eligibility criteria for steroid switch, we found: PSA progression without any radiological or clinical progression during abiraterone acetate + prednisone; no high-grade adverse events related to CYP-17 inhibition; and unfitness for chemotherapy or radium-223.

Conclusion Although large randomized prospective trials are warranted, steroid switch seems to off a good option for certain patients treated with abiraterone acetate plus prednisone or prednisolone.

Keywords Dexamethasone · Prednisone · Abiraterone · Switch

Introduction

Prostate cancer is one of the most common causes of cancer-related death in the western world [1]. In recent years, therapeutic management of prostate cancer has significantly changed for both metastatic and non-metastatic castration-resistant prostate cancer (CRPC), as well as for hormonal-naive patients [2]. Since 2010, five novel drugs with different mechanisms of action have shown to increase survival [2]. However, no agent is curative and inevitably all treated patients will evolve into disease progression.

Abiraterone acetate (AA) is a CYP17 inhibitor which blocks the synthesis of androgens. CYP17 catalyzes the conversion of pregnenolone and progesterone to testosterone precursors, dehydroepiandrosterone and androstenedione. Since CYP17 impacts the production of glucocorticoids, the levels of cortisol fall, and the organism produces adrenocorticotropic hormone (ACTH) as a compensatory strategy. This induces an increase in the mineralocorticoid levels, even if aldosterone itself is suppressed. The rise in ACTH can be hampered with the concomitant administration of steroids. Thus, AA is administered in combination with prednisone or prednisolone 5 mg twice daily [3, 4] to prevent the secondary mineralocorticoid excess related to the blockade of CYP17 [5]. However, prednisone or prednisolone are not the only concomitant steroids added to AA. Some clinical trials have investigated the combination of dexamethasone with AAand reported clinical effi [6]. Based on these results, diff ent studies have investigated the possibility of a 'steroid switch' (SS) from prednisone to dexamethasone in patients who progress on AA plus prednisone or prednisolone. The aim of this review is to report on the currently available data on the topic, examining potential scenarios for the corticosteroid switch.

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Role of abiraterone acetate in CRPC

Abiraterone acetate has been the fi t hormonal agent to improve the survival of patients with metastatic CRPC [3]. Two phase III, multinational, double-blind, randomized, placebo-controlled trials established the effi and safety of the combination of AA with prednisone in metastatic CRPC [3, 4]. The fi t study, COU-AA-301, involved patients who previously received docetaxel, while the second study, COU-AA-302, involved only patients who had not received any chemotherapy previously and did not have clinically signifi cancer-related symptoms (i.e., asymptomatic or minimally symptomatic patients). Both studies enrolled a large number of patients (more than 1000) and had overall survival as the primary endpoint (co-primary in COU-AA-302). Secondary endpoints included toxicity and diff ent events related to the progression of the disease. The fi analysis of COU-AA-301 estimated 4.6 months improvement in overall survival (15.8 months for AA versus 11.2 months for prednisone + placebo) [7] while the COU-AA-302 confi med also an improvement in survival (4.4 months with 34.7 months for AA versus 30.3 in the placebo group, respectively) [8]. In addition, all secondary end-points were in favour of the combination of AA with prednisone compared to placebo with prednisone. Finally, COU-AA-301 and COU-AA-302 confi med the higher incidence of adverse events associated with mineralocorticoid activity with AA plus prednisone in comparison to prednisone alone [9]. A signifi increasing of all-grade hypertension (risk ratio (RR) = 1.53), cardiac disorders (RR = 1.47), liver function test abnormalities (RR = 1.93), hypokalaemia (RR = 1.56), grade ≥ 3 adverse events, cardiac disorders (RR = 1.55) and hypokalaemia (RR = 4.23) has been observed in favour the CYP-17 inhibitors compared to compared with placebo. Based on these studies, the combination of AA with prednisone is approved for the treatment of patients with metastatic CRPC.

The basis for the "steroid switch"

During AA-based therapy, inhibition of androgen synthesis is achieved by blocking the CYP17, key enzyme responsible for adrenal and intratumoral androgen synthesis from pregnenolone. In addition, a corticosteroid drug must be administered during treatment to avoid side effects. Corticosteroids have been widely used in CRPC. Their antitumour eff is assumed to be due to the reduction in the synthesis of adrenal androgens via ACTH production suppression [10, 11]. For this reason, all corticosteroids, including hydrocortisone, prednisolone and dexamethasone were thought to be equally effective [11]. Even though numerous explanations have been proposed, the exact mechanism for the SS effect is still poorly understood (Fig. 1).

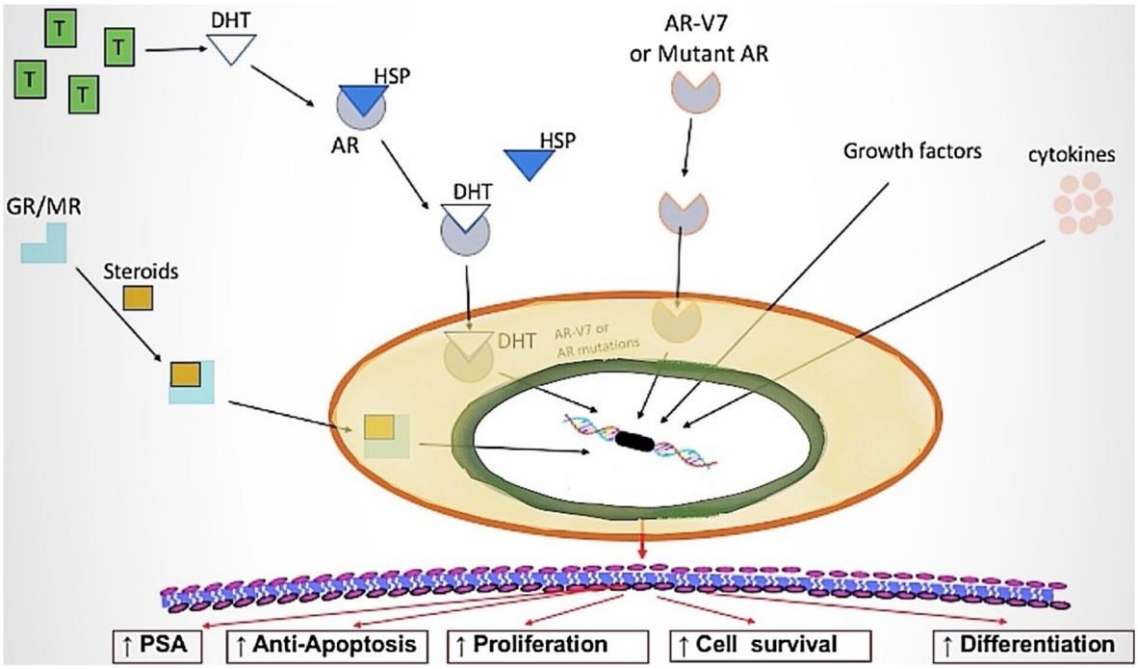

Fig. 1 Pathway that are involved in the 'steroid switch': *GR* glucocorticoid receptor, *TGF* transforming growth factor, *MR* mineralocorticoid receptor, *VEGF* vascular endothelial growth factor, *HGF* hepatocyte growth factor, *IL* interleukin, *AR* androgen receptor

Different glucocorticoid receptor (GR) activation between prednisolone and dexamethasone may explain the SS effect. Patients affected by prostate cancer who underwent androgen deprivation therapy showed a significant increase in GR expression [12]. Androgen receptor (AR) and GR belong both to the nuclear steroid receptor family and have similar structure and function, also sharing some of their transcriptional targets [12, 13]. Several hypotheses on AR and GR receptor interaction have been presented. AR inhibition activates GR, which binds to the nuclear androgen response elements and controls AR target genes, thereby bypassing the AR pathway [12, 13]. With the progression of CRPC over time, prednisolone can increasingly turn on the GR receptor and this effect could be reversed by switching to dexamethasone, which happens to have decreased affinity for GR.

Differences in mineralocorticoid receptor (MR) activation between prednisolone and dexamethasone might also aff effi , even though only few studies have investigated the role of MRs in CRPC [14]. The glucocorticoid resistance which takes place once MR is activated might be counteracted with a 'SS' to dexamethasone, which has less affi for MR receptor [14]. MR is expressed in prostate tumour cells independent of AR and seems to be controlled by inflammatory cytokines, which in turn are involved with prostate cancer progression [15]. Changes in MR expression, as a result of inflammatory cytokines, are thought to be implicated in prostate cancer carcinogenesis [16].

It is also possible that corticosteroid-responsive AR mutations, activated by prednisolone but not dexamethasone, may be responsible for the occurring resistance. It is speculated that the effect of ligands other than testosterone might be a result of AR mutations in the hinge and/or ligand-binding domain [17]. Some studies have reported AR mutations triggered by corticosteroids, dexamethasone and prednisolone included [18, 19].

Acting on the modulation of cellular growth factors, cytokines and transcription factors, which might also lead to differences in the activity against the tumour, glucocorticoids play an anti-inflammatory and anti-angiogenic role in prostate cancer [20, 21]. Dexamethasone elicits an anti-angiogenic effect on prostate cancer, by lowering the expression of vascular endothelial growth factor, IL-6 and IL-8, via activation of the GR-mediated pathway [22, 23]. IL-6 has been shown to stimulate prostate tumour cells replication via GR in an androgen-independent way and to activate the AR via STAT3-dependent signalling [24]. Moreover, modifications in IL-6 serum levels correlated with dexamethasone in CRPC patients [25].

Finally, differences in pharmacokinetics between prednisolone and dexamethasone have been observed. Dexamethasone might cause a stronger ACTH suppression due to its longer half-life and a more efficient activity against cancer than prednisolone [26]. Dexamethasone might reduce mineralocorticoid activity while exerting a more potent glucocorticoid activity than prednisone [27].

Clinical experience of SS

To date, only few studies showed the efficacy of SS in CRPC (Table 1) [28–31]; all studies involved patients with metastatic CRPC who progressed after AA + prednisone and

Table 1 Patients characteristics of included studies

Study author	Nature	Previous lines of treatment	Numberof patients	Median age (range)	% ECOG (0–1)	% Gleason score ≥ 8	% Patients with visceral metastasis	Median serum PSA (µg/l or ng/ml)
Lorente et al. (2014)	Retrospective	Chemotherapy	30	68.9 (NR)	90	NR	3.3*	199.5 (9.7–2689)
Fenioux et al. 2018	Retrospective	7 patients received docetaxel	48	82.33 (56.47–94.00)	73	62.5***	4.1	42.85 (5.20–1 275)
Romero-Laorden et al. SWITCH (2018)	Phase II prospective study	1 median number of prior treatment lines for CRPC	26	73.0 (60–85)	96	54	15	36.1 (4.46–965.2)
Loviello et al. (2018)	Retrospective	3 median number of prior treatment lines for CRPC	36	76 (62–85)	83	47	25	88 (4–1550)

NR not reported, *CRPC* castration resistant prostate cancer

*Patients with bone and visceral metastasis

**7 Patients received docetaxel

***Gleason > = 7

Table 2 Efficacy of steroid switch

Study author	Median duration of previous AA + P	Time to PSA progression median	PFS median	OS median	Best PSA response (%)
Lorente et al. (2014)	6.3 months	11.7 weeks	NR	NR	≥50% (20)
Fenioux et al. (2018)	8.9 months	10.35 months	NR	NR	≥50% (48)
Romero-Laorden et al. (2018)	5.8 months	NR	11.8 months	20.9 months	≥50% (35)
Roviello et al. (2018)	2.4 months*	NR	10.8 Weeks	17.6 Weeks	≥50% (11)

NR not reported

*Reported as 9.9 weeks

switched to AA + Dexamethasone. The results of the four studies are summarized below and in Tables 1 and 2.

Preliminary data on SS date back to the 2014 retrospective study performed by Lorente et al. [28] where 30 patients affected by CRPC switched from twice daily 5 mg of prednisone/prednisolone to once daily 0.5–1 mg of dexamethasone after PSA progression. The progression of PSA was categorized as an increase of 25% over the nadir and confirmed by an additional read after 3 weeks at the earliest. The first AA in combination with prednisone/prednisolone was given for 27.7 weeks average time to patients (95% CI 11.7–124.4) whereas the following AA + dexamethasone was administered for 20.6 weeks of average time (95% CI 16.2–24.9). Six patients (20%) achieved a confirmed PSA decrease of > 50% while 11 patients (39%) reached a satisfactory PSA decrease of ≥ 30%. The average time to PSA progression was 11.7 weeks (95% CI 8.6–14.8) in the total cohort administered with AA + dexamethasone, and 27.6 weeks (95% CI 14.5–40.7) in patients with a confirmed decreased of PSA value of at least 50%. According to RECIST criteria, fi e patients accomplished a stable disease state and two patients reported a partial response. Although one patient returned to prednisolone due to a grade 2 hypotension, no grade 3 and grade 4 adverse events were reported, and the therapy was well tolerated.

In 2018, Fenioux et al. reported the data of a retrospective analysis on patients with metastatic CRPC who switched from AA + prednisone10mg daily to AA + dexamethasone (0.5 mg daily) after PSA progression without any radiological or clinical sign of disease [29]. A total of 48 patients underwent SS. A median progression-free survival of 10.35 months (95% CI 4.83–15.21) was observed after SS. Thirteen (48.15%) patients had a PSA response. Based on the multivariate Cox analysis, the authors established a prognostic model, identifying 3 levels of risk (low, intermediate and high), defined by PSA level at the time of SS and hormone sensitivity. Treatment with AA + dexamethasone was well tolerated with no grade 3 or 4 toxicity reported after SS.

The SWITCH study (NCT02928432) was a prospective multicenter study conducted at four university hospitals in Spain. This was the first prospective study reporting data on SS [30]. This study enrolled patients who progressed on AA + prednisone (biochemical progression or limited radiological progression). The primary endpoint was measured as the proportion of patients achieving a PSA decline of ≥ 30%. A total of 26 metastatic CRPC patients were enrolled. All patients had PSA progression and 12 (46.2%), also presented a limited radiological progression as defi in the study inclusion criteria. A decline of PSA > 30% and > 50% was observed in 12 (46.2%) and 8 (35%) of the enrolled patients, respectively. Median PSA progression from SS was 5.3 months (95% CI 3.1–7.5) and a moderate but signifi correlation was observed with the prior response to AA + prednisone ($p = 0.001$). Two radiological responses were observed. The median time to radiographic progression after the SS was 11.8 months (95% CI 6.6–17.1) and overall survival was 20.9 months (95%CI 10.0–31.7). No grade 3–4 related adverse events were reported. Interestingly, the authors performed a biomarker study showing that patients with normal status androgen receptor in circulating tumour DNA respond to SS.

The safety and activity of SS in patients affected by advanced, pre-treated CRPC who progressed after AA treatment, was assessed by a further retrospective and small study in 2018 [31]. Thirty-six patients were administered with oral daily AA + 0.5 mg dexamethasone until unacceptable toxicity or disease progression. The study reported a median progression-free survival of 10.8 weeks (95% CI 9.2–16), a median survival of 17.6 weeks (95% CI 15.8–28.8) and a ≥ 50% decrease of PSA in 4 patients (4%) albeit greater survival and effi has been shown for the subgroup of patients treated for more than 3 months with AA. No grade 3 and 4 adverse events were reported, and the therapy was well tolerated.

Finally, data from a randomised phase II trial compared the efficacy of prednisone at the standard dose and dexamethasone in chemotherapy-naïve patients with CRPC [12]. The study showed that 7 of the 19 (37%) evaluable cases had a confi med PSA response to dexamethasone when a crossover from prednisone to dexamethasone was performed at PSA progression.

Table 3 Eligibility criteria for SS in metastatic CRPC patients

Main
PSA progression without any radiological or clinical progression during Abiraterone acetate + prednisone
No adverse events of related to resistant CYP-17 inhibition
Patients unfit for chemotherapy or Radium-223
Secondary
> 50% PSA response to prior abiraterone acetate + prednisone
Limited radiological progression
≤ 3 new asymptomatic metastasis in bone scan,
No new soft tissue lesions,
< 40% increase in the size of target lesions according to RECIST criteria
Short time to PSA progression (<6 months)

Better patient selection

Abiraterone acetate has been the fi t hormonal agent to achieve a survival benefit in metastatic CRPC patients. The SS off the opportunity to prolong the treatment with AA in a non-expensive, safe fashion. However, there is a need for better identifi of the patients who may benefit from SS. To date, all published studies, except from 2, evaluated patients with PSA progression without any radiological or clinical progression [30, 31]. Therefore, in the absence of specific guidelines, it seems that the best candidate to a SS during AA + prednisone is the patient with PSA progression alone, while the role of SS in patients with limited radiological progression is still unclear.

Another important issue is to identify patients who may benefi from SS in relation to the duration and effi of prior AA+ prednisone. Although one study appears to demonstrate that short time to PSA progression (<6 months) on AA + prednisone is a positive prognostic factor during subsequent SS [29], the SWITCH study reported a correlation between biochemical PFS on AA + dexamethasone and biochemical PFS on AA + prednisone. In addition, the percentage of PSA response during SS was 41.7% and 21.4%, respectively, in patients with or without previous PSA response on AA + prednisone [30]. In line with these data, another study showed that the efficacy and survival during SS correlated with prior AA duration [31]. However, more data is needed to understand the role of prior AA + prednisone as a prognostic factor during SS.

Other possible favourable prognostic factors are the long duration of response to hormone therapy (>5 years) and low PSA level (<50 ng/mL) at the time of SS [29]. Finally, the prior use of docetaxel does not appear to correlate with radiographic PFS [29].

Furthermore, there is the important question of what therapy to administer after SS. In this context, only two studies reported data on overall survival, and on this basis, it appears that either chemotherapy or radium-223 (if possible) is the best approaches in patients who progressed after SS. However, both safety and efficacy of these drugs after a progression of disease on a prior treatment of AA + prednisone and subsequent SS are still to be defined. Table 3 reports possible eligibility criteria for SS.

Only one study performed biomolecular analysis to identify possible predictive factors [30]. It has been reported that biochemical PFS, PSA response and radiographic PFS are lower in patients with androgen receptor mutations [30]. It must be noted that such type of therapy is most eff e in those patients whose androgen receptor is not mutated nor alternatively spliced. One of the most common features of CRPC is a splice version of the androgen receptor (AR-V7), which constitutively activates

Fig. 2 Possible study consort diagram. *Including patients without any radiological or clinical progression; patients with no high grade adverse events related to CYP-17 inhibition. *AA* Abiraterone acetate, *P* prednisone, *D* dexamethasone

the receptor, therefore bypassing the need for androgens and invalidating any androgen deprivation approach [33].

It is common practice to maintain therapy with novel hormonal agent beyond PSA rise, until radiological and/or clinical progression of the disease [34]. For this reason, the SS may be an optimal and much less expensive strategy in patients who had a PSA progression during AA + prednisone. In addition, the SS may be a good option for patients unfi for chemotherapy and not eligible for Radium-223, as its effi and duration of response are comparable to those of enzalutamide after AA in CRPC treatment [35]. Unfortunately, all except for one of the studies reported in our review, are retrospective, with incomplete information and small sample sizes (a total of 146 patients). The data, therefore, cannot be considered conclusive. Large randomised prospective trials are warranted to determine the usefulness and the impact on survival of SS in CRPC patients with PSA progression during AA + prednisone. An example of design for a possible trial is reported in Fig. 2. Based from the assumption that SS might be recommended to patients treated with AA + prednisone without any radiological or clinical progression, the study should investigate the SS in men treated with AA + prednisone who perform PSA progression without any radiological or clinical progression and with no high-grade adverse events related to CYP-17 inhibition. After PSA progression, patients should be randomized to receive AA + dexamethasone or continue AA + prednisone until the further PSA progression or radiological or clinical progression of disease. In conclusion, best sequence of treatment in CRPC is still unclear [36, 37], SS seems to off a good option for certain patients treated with AA + P.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics 2018. CA Cancer J Clin. 68:7–30
2. Crawford ED, Petrylak D, Sartor O (2017) Navigating the evolving therapeutic landscape in advanced prostate cancer. Urol Oncol. 35S:S1–S13
3. de Bono JS et al (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995–2005
4. Ryan CJ et al (2013) Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138–148
5. Attard G, Reid AH, Olmos D et al (2009) Antitumor activity with CYP17 blockade indicates that castration-resistant prostate cancer frequently remains hormone driven. Cancer Res 69:4937–4940
6. Dizdar O (2015) Is dexamethasone a better partner for abiraterone than prednisolone? Oncologist 20(5):e13
7. Fizazi K, Scher HI, Molina A et al (2012) Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 13(10):983–992. (**Erratum in: Lancet Oncol. 2012 Nov;13(11):e464. Lancet Oncol. 2014 Aug;15(9):e365**)
8. Ryan CJ, Smith MR, Fizazi K et al (2015) Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16(2):152–160.
9. Roviello G, Sigala S, Danesi R et al (2016) Incidence and relative risk of adverse events of special interest in patients with castration resistant prostate cancer treated with CYP-17 inhibitors: a meta-analysis of published trials. Crit Rev Oncol Hematol 101:12–20
10. Eichholz A, Ferraldeschi R, Attard G et al (2012) Putting the brakes on continued androgen receptor signaling in castration-resistant prostate cancer. Mol Cell Endocrinol 360:68–75
11. Khandwala HM, Vassilopoulou-Sellin R, Logethetis CJ et al (2001) Corticosteroid-induced inhibition of adrenal androgen production in selected patients with prostate cancer. Endocr Pract 7:11–15
12. Crona DJ, Whang YE (2017) Androgen receptor-dependent and independent mechanisms involved in prostate cancer therapy resistance. Cancers (Basel) 9: pii: E67
13. Arora VK, Schenkein E, Murali R et al (2013) Glucocorticoid receptor confers resistance to antiandrogens bybypassing androgen receptor blockade. Cell 155:1309–1322
14. Lan NC, Graham B, Bartter FC et al (1982) Binding of steroids to mineralocorticoid receptors: implications for in vivo occupancy by glucocorticoids. J Clin Endocrinol Metab 54:332–342
15. Dovio A, Sartori ML, De Francia S et al (2009) Diff ential expression of determinants of glucocorticoid sensitivity in androgen-dependent and androgen-independent human prostate cancer cell lines. J Steroid Biochem Mol Biol 116:29–36
16. Leach DA, Powell SM, Bevan CL (2016) Women in cancer thematic review: new roles for nuclear receptors in prostate cancer. Endocr Relat Cancer 23:T85–T108
17. Taplin ME, Bubley GJ, Shuster TD et al (1995) Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 332:1393–1398
18. Zhao XY, Malloy PJ, Krishnan AV et al (2000) Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. Nat Med 6:703–706
19. Richards J, Lim AC, Hay CW et al (2012) Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res 72: 2176-2182
20. Nishimura K, Nonomura N, Satoh E et al (2001) Potential mechanism for the eff of dexamethasone on growth of androgen-independent prostate cancer. J Natl Cancer Inst 93:1739–1746
21. Lam JS, Leppert JT, Vemulapalli SN et al (2006) Secondary hormonal therapy for advanced prostate cancer. J Urol 175:27–34
22. Yano A, Fujii Y, Iwai A et al (2006) Glucocorticoids suppress tumor angiogenesis and in vivo growth of prostate cancer cells. Clin Cancer Res 12:3003–3009
23. Akakura K, Suzuki H, Ueda T et al (2003) Possible mechanism of dexamethasone therapy for prostate cancer: suppression of circulating level of interleukin-6. Prostate 56:106–109

24. Ueda T, Bruchovsky N, Sadar MD (2002) Activation of the androgen receptor N-terminal domain by interleukin-6 via MAPK and STAT3 signal transduction pathways. J Biol Chem 277:7076–7085
25. Komiya A, Shimbo M, Suzuki H et al (2010) Oral low-dose dexamethasone for androgen-independent prostate cancer patients. Oncol Lett 1:73–79
26. Diederich S, Scholz T, Eigendorff E et al (2004) Pharmacodynamics and pharmacokinetics of synthetic mineralocorticoids and gluco-corticoids: receptor transactivation and prereceptor metabolism by 11beta-hydroxysteroid-dehydrogenases. Horm Metab Res 36:423–429
27. Nishimura K, Nonomura N, Yasunaga Y et al (2000) Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. Cancer 89:2570–2576
28. Lorente D, Omlin A, Ferraldeschi R et al (2014) Tumour responses following a steroid switch from prednisone to dexamethasone in castration-resistant prostate cancer patients progressing on abiraterone. Br J Cancer 111:2248–2253
29. Fenioux C, Louvet C, Charton E et al (2018) Switch from abiraterone plus prednisone to abiraterone plus dexamethasone at asymptomatic PSA progression in patients with metastatic castration-resistant prostate cancer. BJU Int
30. Romero-Laorden N, Lozano R, Jayaram A et al (2018) Phase II pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mCRPC) patients with limited progression on abiraterone plus prednisone (SWITCH study). Br J Cancer
31. Roviello G, Petrioli R, Bonetta A et al (2018) Corticosteroid switch in heavily pre-treated castration-resistant prostate cancer patients progressed on abiraterone acetate plus prednisone. Invest New Drugs 2018
32. Venkitaraman R, Lorente D, Murthy V et al (2015) A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. Eur Urol 67:673–679
33. Sobhani N, Generali D, D'Angelo A et al (2018) Current status of androgen receptor-splice variant 7 inhibitor niclosamide in castrate-resistant prostate-cancer. Invest. New Drugs. https://doi.org/10.1007/s10637-018-0653-2
34. Gillessen S et al (2015) Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol 26:1589–1604
35. James ND, Sydes MR, Clarke NW et al (2016) Addition of docetaxel, zoledronic acid, or both to fi t-linelong-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. Lancet 387:1163–1177
36. Francini E, Petrioli R, Roviello G (2014) No clear evidence of a clinical benefi of a sequential therapy regimen with abiraterone acetate and enzalutamide. Expert Rev Anticancer Ther 14(10):1135–1140
37. Petrioli R, Francini E, Roviello G (2015) Is there still a place for docetaxel rechallenge in prostate cancer? World J Clin Oncol 6(5):99–103